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# PROTEINURIA: THE STORY OF 280 YEARS OF TRIALS, ERRORS, AND RECTIFICATIONS

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FROM the development of any subject in our texts the student of medicine can learn how easy it is for shrewd, scholarly physicians to make the same plausible errors that great statesmen, generals, and natural scientists have made. The wisest men can have intuitions and obtain information which seems to confirm them; from this they and their associates accept invalid theories or embark on disastrous courses of action. Pasteur's career exemplifies the opposite, almost superhuman, type of thinking. His guiding principle was: "Keep your enthusiasm, but let strict verification be its constant companion." The history of our thinking about proteinuria is a classic example of the errors that our elders and betters made by neglecting verification.

In the 1690s Frederik Dekkers of the Netherlands thought that wasting diseases might be due to bodily substances leaking away in the urine. After examining a few samples of urine from such patients, he reported that the specimens tasted sweet. When they were boiled with added acetic acid, a coagulum settled out and an oily layer rose to the surface. Thus Dekkers proved that all the elements of milk were being lost in the urine. Since the experiment confirmed his hypothesis, the learned and renowned Dutch doctor made no similar tests of urine from other patients.[1]

Seven decades later, Domenico Cotugno, in Naples, did the heat-and-acetic-acid test on urine passed by an edematous man in response to a diuretic, potassium bitartrate. A large precipitate formed, just as happened when the test was done on blood serum or edema fluid. This proved to Cotugno that the drug had moved edema fluid into the urine, which normally gave negative tests. It also confirmed his belief that sciatica was due to edema of the nerve sheath. Cotugno had been the first to prove that the cerebral ventricles and spinal canal contained not "vapor," as had been universally taught, but a colorless fluid which reacted negatively to the heat-and-acetic-acid test. He made no study of the urine in other cases of dropsy before giving a diuretic, since his experiment had confirmed his concept of the origin of sciatica.[2] He was highly regarded as a clinician, and his observation was passed on to British physicians by Erasmus Darwin, a brilliant contemporary.[3]

William Charles Wells, a physician who had elucidated the method by which dew or frost forms on cloudless nights, observed the relation of proteinuria to scarlet fever and concluded that it was due to peritoneal irritation. But he did note that kidney disease was present in cases of dropsy unrelated to scarlatina.[4] Wells also was the first to state clearly the theory of evolution by the natural selection of men or animals best adapted to their environment. That he should have mistaken the source of one type of proteinuria proved once again that "to err is human" and that the "wisest man contains a fool."

John Blackall was the first to make systematic studies of albuminuria. He noted that "the coagulation of the urine takes place long before the boiling heat; it is not a temporary relief but a continued symptom of dropsies through their whole course." He quoted Cotugno and Darwin, but noted that if they had made more observations they would have learned that "the curative effort of Nature is not urine loaded with serum, but almost devoid of it."[5]

One hundred and thirty years after proteinuria was first reported, Richard Bright established its relation to renal disease[6] and his colleague John Bostock showed how loss of protein through the urine could lead to a decrease in the quantity of protein in the blood.[7] A century later this was fully confirmed by electrophoretic analysis of the blood and urine of patients with Bright's disease.[8]

Microscopic study of the urine and the kidneys of patients with proteinuria showed that severe tubular lesions were always present. While glomerular disease was severe in patients who had died in uremia, it was mild or absent in those with massive proteinuria and edema. In such cases fatty degeneration of tubules was most striking, and casts with fat-laden cells appeared in the urine. Many of us were taught that in lipoid nephrosis tubular disease led to protein loss, similar to the production of nasal or bronchial secretion rich in protein. With better staining methods, glomerular lesions were always detected—at least in some tufts of some glomeruli—in all these cases. But many pathologists thought these might be artifacts, caused by queer technical methods, or that these were not the same sort of cases in which they saw only normal glomeruli. Only when the electron microscope revealed changes in every tuft of every glomerulus in pure lipoid nephrosis was the possibility of the glomerular primacy in proteinuria conceded. Before this occurred, experiments in animals had shown that glomerular hyperpermeability led to secondary changes in the tubules.

Early in the 17th century William Harvey learned in Padua that blood circulated through imperceptible channels in the lungs and solid tissues. The hypotheses concerning circulation which Colombo, Servetus, and Cesalpino developed were anathema to Rome; devout men had killed Colombo and Servetus by due process of ecclesiastical law. Hieronymus Fabricius ab Aquapendente published his observations on the valves in veins and the heart. Although he drew no conclusions in print about the circulation, one of his illustrations was copied in Harvey's book.

In England it was safe to utter heretical opinions, but Harvey sought verification by experiments on snakes and dogs. These satisfied him and immortalized his name, but many distinguished contemporaries scoffed at such circumstantial evidence. Man was neither snake nor dog. During the past three centuries this argument has pleased many physicians in relation to animal experiments on tuberculosis and on occlusive arterial disease. Animal experiments had also explained proteinuria and suggested the source of lipid in the serum and renal tubules of patients who had the nephrotic syndrome. Few pathologists noticed these experiments and they are not cited in textbooks.

Govaerts used salamanders as Harvey had used snakes. In these urodeles some nephrons have stomata which connect with the peritoneal cavity. Fine particles or large organic molecules injected into the peritoneal cavity were observed to accumulate in the tubule cells distal to such stomata, but not in nephrons lacking stomata. After being injected into a vein or the peritoneal cavity, molecules of smaller size passed through the glomerular membrane and accumulated in the tubules of all nephrons.[9]

The hypothesis of glomerular filtration and tubular reabsorption of proteins was tested in mammals by means of a dye—Evans blue—which conjugates firmly with serum albumin. When given intraperitoneally to normal rats, the dyed albumin slowly accumulates in very small amounts in the tubules, but no blue tint appears in the urine. When the dye is injected in the same dose into rats with chronic proteinuria, the urine promptly turns deep blue and the tubules are filled with dark blue cytoplasmic clumps.[10] When mammalian kidneys are perfused with ice-cold plasma, the flow of urine increases greatly; its dextrose content is the same as that of the perfusate,[11] while the protein content is only 20 mg.% and that of the perfusate is 5 gm.%.[10] Such studies indicate that while a healthy man's glomeruli are barely permeable to albumin, his daily glomerular filtrate of 180 l. permits 25 gm. of albumin to enter the tubules. This is all reabsorbed along with 200 gm. of dextrose. Proteinuria or glycosuria occur when the reabsorptive capacity of the tubules is exceeded; protein or glycogen then accumulates in the tubule cells. The tubular changes of nephrosis are not the cause but the result of excessive leakage of albumin and of lipoprotein through the glomeruli. Dekkers' observation and Govaert's hypothesis have been brought up to date in a most elegant presentation.[12]

In the nephrotic syndrome the plasma cholesterol and triglycerides rise as the serum albumin falls. At the same time that lipid is accumulating in the tubules, the concentration of lipoprotein in the urine rises.[8] This is in striking contrast with the simultaneous fall of cholesterol and albumin in the blood in cirrhosis of the liver. Perhaps the nephrotic patient has damage to hepatic as well as to renal capillaries, and this stimulates the production of lipid. This aspect seems not to have been explored by comparative study of hepatic and renal biopsies.

Dogs became edematous when subjected to repeated plasmapheresis, which markedly lowers serum albumin. In each of three studies some edematous dogs developed hypercholesterolemia. In one dog cholesterol rose from 166 to 409 mg./dl. as albumin fell from 4 to 1.3 gm./dl.[13] In earlier studies[13a] the most marked rise was from 100 to 216 mg./dl. as albumin fell from 2 to 0.95 gm./dl. When rats were injected under the skin with Freund's adjuvant plus liver suspensions, there was no significant fall in albumin or rise in lipids in the plasma. But when kidney suspensions were given in the same way, all the rats developed severe proteinuria, a drop in serum albumin, and a rise in lipids.[14] The rats with the lowest albumin levels had the highest lipid levels. Cholesterol rose from less than 100 mg./dl. in controls to more than 500 mg. and total lipids rose from 300 mg./dl. to more than 1,800, as the albumin fell to less than 30% of control levels. Fall in serum albumin, not hepatic "irritation" by antigen-antibody complexes, seems to be the cause of nephrotic hyperlipidemia.

Fatty acids are transported in the blood firmly bound to albumin, but if albumin is low there would be an increase in the amount of fatty acids present as sodium or potassium salts. At *p*H 7 there can be no "free fatty acid." Soap is a sodium or potassium salt of fatty acid, so a fall in serum albumin could raise the level of surface-active substance (or detergent) in the plasma. When a synthetic detergent is given intravenously, a prompt, marked rise in cholesterol and total lipid follows.[15] Alcohol, another surface-active substance, if ingested in quantities leading to coma, causes an equally sharp, sustained rise in plasma cholesterol and lipids.[16] With retention of bile salts, which are powerful detergents essential to the absorption of lipid, there is also marked hyperlipidemia in the absence of liquid uptake from the intestine. Experiments can be designed for strict verification of the hypotheses on causation of hyperlipidemia in nephrosis. Without such studies the source of the lipid reabsorbed by the tubules cannot be determined. One crucial experiment would be the continuous infusion of dilute solutions of sodium stearate into the splenic veins of rabbits or dogs. This would give maximal stimulation to hepatic cells with minimal rise in the level of detergent in other tissues. If such experiments fail to evoke hyperlipemia, the hypothesis is invalid and other mechanisms must be sought.

Even if some hypothetical explanation for renal hyperlipidemia is confirmed, the real mystery remains. What causes the glomerular injury in each case? It will not do to say an autoimmune reaction, or antigen-antibody-complement-fibrin deposited in the basement membrane. Why does patient A—given tridione for fits or gold salts for arthritis, or with malaria, syphilis, or a viral or bacterial infection—develop this syndrome, while patients B through Z, with the same "cause," have either transient proteinuria or none at all? Until we know why "many are called but few are chosen," we shall not know the pathogenesis of proteinuria with accumulation of lipid in the tubules.

Dekkers' erroneous guess about marantic wasting, Cotugno's guess about the relation of sciatica to proteinuria after diuresis, and Wells' guess that scarlatina led to peritoneal irritation and thus to proteinuria are classical examples of enthusiasm without strict verification. By studying the story of proteinuria, medical students can learn how often very good physicians have been badly fooled by having intuitions confirmed.

In my case this study began with translating Cotugno; I did this when I was a senior in high school. When I was a freshman in medical school I read the history of proteinuria. I learned that Cotugno was not the first to observe proteinuria, as I had been told by a learned professor of medicine. I also realized how many fine men went astray before Bright and Bostock sought strict verification. This taught me not to believe my own guesses until my initial experiments had been confirmed by other investigators. The mammalian experiments on proteinuria,[10] to verify Govaert's observations on salamanders, were performed 30 years after my introduction to proteinuria. I was relieved to find confirmation in Thorn's studies of the increased severity of protein loss when nephrotics were given 50 gm. of human albumin intravenously each day.[17] Both nitrogen loss and protein loss rose sharply, with only a transient rise in serum albumin. Thorn's work also was confirmed when Kempner[18] showed that serum albumin rose as proteinuria decreased in nephrotic children on diets very low in protein as well as in salt and food allergens—diets containing no wheat, milk, eggs, chocolate, or orange juice.

I am not surprised that many good physicians still treat nephrotics with high protein diets 30 years after the crucial experiments of Thorn and Kempner. They would rather not wait to see what happens after two weeks on rice and apple sauce, with the gradual addition of other food if proteinuria had decreased and serum albumin had risen. Patients as well as physicians prefer large doses of corticosteroid, or cytotoxic agents, to any change in diet. The state of our knowledge of the mechanisms of glomerular damage has advanced greatly;[19] perhaps this will lead to unlocking the secret of prevention and early cure.

Thus ends 280 years of trials and errors in the study of the coagulable part of the serum in the urine. The story taught one student of medicine to seek strict verification of notions, diagnoses, and conclusions. This set a standard he has often failed to meet. He can end the tale with a cheerful view of our profession, written by an 18th century poet: "Healers of men they're called and we confess/Theirs the long study, theirs the lucky guess," or with the realistic appraisal of a 20th century dramatist: "Your doctor is no more a scientist than your tailor." (In Shaw's day doctors made house calls because they knew that until a doctor had seen a patient in his home, with his family, he knew no more about him than a naturalist who has only seen birds and beasts in cages. Tailors do not make house calls, but Dekkers, Cotugno, Wells, and Blackall saw most of their patients in their natural habitats.)

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Note: Translations of Dekkers[1] and of Cotugno[2] and quotations from Blackall[5] are given in Dock, W.: Early observers of albuminuria. *Ann. Med. Hist.* *4*:287-90, 1922.

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